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Barring recurrence, lymphedema is the most dreaded sequelae of breast cancer treatment. Nevertheless, there have been no cohort studies or comprehensive studies of large numbers heretofore. We built upon an existing data base on a cohort of consecutively treated patients from 1976 to 1978. Of the 543 ten-year recurrence-free survivors: 165 are dead; 64 cannot speak or refused; 42 are lost to followup; 272 women are study subjects on whom circumferential arm measurements and interviews were obtained. We evaluated physical characteristics, cancer characteristics and specific intraoperative and early postoperative treatment variables and many factors present in the subsequent years, including specific illnesses, general medical status, contralateral breast cancer development, activity in housework, occupation, and leisure, arm exercise, infection and injury. The incidence of any measurable lymphedema in these long-term survivors was 27%, whereas 11% had lymphedema causing a 2 inch greater circumference on the treated side. Of the 28 factors evaluated, only two were statistically significantly associated with lymphedema: the history of infection or injuries requiring antibiotics and amount of weight gain since treatment. In summary, women should continue to be counseled and perhaps advised even more strongly to avoid infections. Furthermore, even though there are many benefits to avoiding weight gain, the predisposition to lymphedema may be another reason.

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FINAL REPORT FOR GRANT NUMBER DAMD 17-94-J-4276

LYMPHEDEMA: INCIDENCE, TIME COURSE AND ETIOLOGY IN LONG-TERM SURVIVORS OF A BREAST CANCER COHORT

TABLE OF CONTENTS

Introduction

Overview of Lymphedema

At least 15% to 20% will develop lymphedema even after modern breast cancer treatment. Lymphedema incidence in five reports published within the last ten years was about 20%.[1-5] The range was 16% to 25.5% of the study populations measured at various intervals after treatment with arm circumferences or volumetric equipment. It is striking that the reported proportion with lymphedema is similar since these patients underwent different procedures for breast cancer treatment in three different countries.

It is estimated that 1-2 million breast cancer survivors are alive today and at least 200,000 of them cope daily with the disfigurement, discomfort and disability of arm and hand swelling. Despite the human cost, lymphedema has not been systematically studied.

Of all the permanent complications of breast cancer treatment, lymphedema is the most troublesome: The cosmetic deformity can not be disguised with normal clothing, physical discomfort and upper extremity disability is associated with the enlargement and recurrent episodes of cellulitis and lymphangitis may be expected in this setting. Added to the physical symptoms is the distress caused unintentionally by the clinicians, interested in cancer recurrence, who trivialize the non-lethal nature of lymphedema.

Parallel studies by the principal investigator

Dr. Jeanne A. Petrek, Principal Investigator, has completed and ongoing protocols involving short and long term complications after breast cancer treatment. (The only major long-term complication is lymphedema.) The research projects concern randomized exercise programs and intraoperative drain techniques and were published in major surgical journals.[6,7] The most recent study has been submitted to a major surgical journal recently and concerns randomization to a postoperative compression dressing.[8] The patients in these prospective research projects are being followed for lymphedema development. They comprise a group of over five hundred patients with prospectively gathered clinical, pathologic, and other variables, including preoperative arm measurements by the research nurse. However, these patients require further follow-up for more meaningful data on lymphedema development since mean follow-up is only 7 years.

Nature and Intent of the Present Work

We examined the incidence, time course, and predictive factors for lymphedema in the long term survivors of a consecutively treated breast cancer cohort.

The current lack of knowledge of factors influencing lymphedema development mandates that all patients be instructed in the same arm and hand care precautions which may be too severe for those at low risk and yet not aggressive enough for those at the highest risk. Furthermore, there has been no evaluation as to the accuracy of those precautions.

The aim of the current project is to investigate factors predictive of lymphedema and to begin to form a scale of risk for lymphedema depending on variables present at initial treatment and in the subsequent years. Prospective studies could then be performed in the future to evaluate and validate the scale of risk. As the long-term objective after those prospective studies, future patients could receive more individualized anti-lymphedema precautions and a specific follow-up schedule for the goal of early detection of this complication depending upon their risk category.

Nevertheless, the first step before considering anti-lymphedema precautions is a scientific evaluation of factors predictive of lymphedema. Heretofore, this has not been accomplished. There has not been any cohort study or otherwise comprehensive evaluation. Lymphedema has merely been cited among other intraoperative and postoperative complications in various series. The scanty scientific evaluation is probably due to the view that issues concerning quality of life are less important than research issues concerning detection, treatment, and recurrence.

Body of Final Report

Experimental Methods:

The women in this study are a subset of 1254 consecutive patients treated for breast carcinoma at Memorial Sloan-Kettering Cancer Center between October 1976 and June 1978 who were recruited for the study of risk factors associated with histologic type of tumor. Personal interviews were conducted by Dr. Ruby Senie, a co-investigator with 1216 (97%) patients during their postoperative hospitalization to obtain epidemiologic data. Tumor size, status of axillary lymph nodes, and other pathologic features of the tumor were assessed by Dr. P. Peter Rosen who reviewed the histologic slides. Height and weight were measured during the physical examination at hospital admission..

Survival analyses have been conducted on 923 of 1216 patients after the following exclusions: primary treatment other than mastectomy with axillary dissection (45 women, 4%), indeterminate size of the primary tumor (91 women, 7%), distant metastases at diagnosis (63 women, 5%), previous treatment for contralateral breast carcinoma (82 women, 7%), height or weight not recorded at admission (5 women, <0.5%), and lack of follow-up information (7 women, <1%).

The study cohort was followed closely for 10 years through annual or more frequent contact with the patients and their physicians. The study subjects are the 543 recurrence-free survivors known alive at 10-years.

Due to the uncompromising emphasis on consistency in the interview process, all study subjects were interviewed by one research nurse, Ms. Margaret Peters.

Much of the research nurse's efforts was directed to finding these patients who, as they age, became less available for easy access to interview and follow-up. Ultimately it was necessary to utilize out-of-hospital sources in the commercial and government sectors for follow-up. Both the National Death Index of the Division of Vital Statistics of the National Center for Health Statistics in Hyattsville MD and Equifax Government and Special Systems, Inc. in McLean VA were utilized.

Study data includes subjective enlargement and self-reported arm circumference measurements, as well as factors previously reported: age, obesity,

extent of dissection, and history of arm cellulitis/lymphangitis. The principal investigator's ongoing prospective studies have suggested: previous arm trauma/surgery without infection, number/proportion of positive lymph nodes, specific intraoperative surgical techniques and the volume/duration of postoperative fluid formation. Factors in the subsequent years involving arm and general activity as well as overall health status, including reconstruction of the ipsilateral mastectomy and possible development of contralateral breast cancer, have never been assessed heretofore. Other factors in subsequent years include occupations, sports, and hobbies, weight change, illnesses, and arm/hand injuries and surgeries.

Computer files from the existing database gathered between 1976 and 1978 of Dr. Ruby Senie and the study data on arm/hand measurements and factors obtained by interview were linked by Dr. Glenn Heller of the Division of Biostatistics of Memorial Sloan Kettering Cancer Center. Then the probability estimates of time lymphedema free were obtained by the product-limit method. The differences between time to lymphedema patterns within a covariate were evaluated by the log-rank statistic.

Addressing tasks in the statement of work and delay of schedule which was officially approved

In the Appendix, please see a copy of the Statement of Work for the project "Lymphedema: Incidence, Time Course, and Etiologic Factors in Long Term Survivors of a Breast Cancer Cohort" that was included in the Army grant application DAMD17-94-J-4276.

Task 1a and Task 1b was achieved with multiple revisions for the appropriate data collecting instruments and returns to pilot testing on non-protocol patients who were being seen for routine follow-up and were similar in age and type of treatment to the study subjects.

Under task 2a and 2b, the actual interviewing process and collection of self-reported measurements has been accomplished on 272 recurrence-free surviving study subjects, the result of which is now the largest study of lymphedema. As evidenced by these numbers, there has been excellent co-operation among those contacted. The self-reported measurements have required more research nurse intervention with follow-up phone calls and reminders than predicted.

The delay in adhering to the Statement of Work occurred in contacting the women who were ten-year survivors but have since been lost to follow-up.

In task 2c, due to the departure of the statistician listed in the grant application, May Nah Ho,MS and the necessity of transferring operations to Glenn Heller, PhD who took her place, there was also several weeks delay.

Task 2d, report at Year 1, was completed on schedule.

In the interim report submitted in October 1996, we provided a preliminary analysis of incidence time course, and factors associated with lymphedema based on those determined to be lymphedematous as defined by their self-reported measurements. A subset of these women, in both lymphedematous and non-lymphedematous category were re-contacted 6 to 9 months later and were asked to repeat the measurements. This special double-check mechanism, not noted as part of the original experimental methods, was created because of the large number of women who stated that their arm was "swollen" but their first set of measurements did not show that the ipsilateral side was 2 cm or more larger in circumference than the contralateral side. In the effort to be inclusive rather than to omit cases, the definition of the group defined to have lymphedema now

consists of three groups of women who we will designate as mild, moderate and severe. The range of these categories is listed under results.

Tasks 3a and 3b were necessarily delayed due to the delay in data acquisition.

Results:

Outline of data collection

Clinical, anatomic, pathologic and treatment variables were obtained prospectively and recorded in the pre-existing database from 1976 to 1978. Data concerning arm infection/injury, physical activity, arm activity/exercise, weight change and life events in the follow-up years were obtained by interview.

The prospectively gathered (in 1978-1978) variables are part of the lymphedema database: height/weight at diagnosis, obesity, menopausal status, previous medical history, medications, cancer primary size, number of lymph nodes excised, number/proportion of lymph nodes excised with metastatic cancer.

Several variables present at time of operation in 1976 to 1978 were not collected at that time but were available from review of medical record. These include various specific intraoperative and early postoperative surgical factors: excision of thoracodorsal nerve complex, excision of pectoralis minor muscle, highest level of lymph nodes excised, and specific data on postoperative fluid formation, such as total volume of drainage and number of days with the drain.

Information obtained from interview consisted of weight changes over the interval from diagnosis to the current time, illnesses, operations, medications, hospitalizations (to confirm the pre-existing database information of the annually updated medical history and cancer status), predominant occupation, hobby, sports in the years since diagnosis (for assessment of general and upper extremity activity level), and arm infection/injury or unrelated arm surgery with detailed data on time of occurrence, length of hospitalization and disability.

Results - overall

Of the original 543 patients known to be alive and breast cancer-free at 10 years, 272 fulfilled all the data points by interview and self-reported arm circumference measurements. The measurement instrument that was validated on non-protocol patients and utilized.

The median age of the 543 ten-year survivors is 75 years. Twenty-five per cent of the 543 ten-year survivors are 83 years or older.

There are 118 patients who are documented to have died. Additionally,

there are 47 women who are thought to have died but more recently and the death cannot be confirmed by the search services which are a minimum of two and a half years behind the current time in the computerization of death certification.

Of the 64 women known to be alive, 40 are considered to be "refusers" due to medical reasons and the inability to be talk and be interviewed. Almost all are living in chronic care facilities. Of the group of 64, there are 24 who are true refusers.

Lastly there are 42 women who may be alive or dead (although the death cannot be documented). These are lost to follow-up.

Results - Incidence

As mentioned in Experimental Methods, in the effort to be inclusive, three categories of lymphedema were devised.

Severe - Greater than or equal to 2 inches between ipsilateral and contralateral arm
Moderate - Some difference but less than 2 inches between ipsilateral and contralateral arm
Mild - No difference in measurements between ipsilateral and contralateral arm

In all of the three above categories of lymphedema, the patients stated at outset of the interview that they believed that they had hand and/or arm swelling as a result of breast cancer treatment.

This three-tier categorization was thought necessary since arm circumference measurements, the most common and only convenient measurement, can be arbitrary. In an underweight woman with thin arms, 2 inches of lymphedematous circumferential enlargement will produce a startling and noticeable difference between her arms and 2 inches represents a great volume of lymph fluid in that woman. In a heavy woman with large arms, 2 inches will represent a lesser volume of lymphedema and can produce no visible difference between her two arms. Furthermore, arm measurements will vary depending on the exact technique used and the tension with which the tape measure is applied.

Lastly, about 10 of healthy unoperated people have up to 1 inch difference between arms, particularly if they possess a large heavy or muscular arm.

Therefore a difference of 1 inch was allowed and categorized as non-lymphedematous unless the patient also stated that she believed that her arm and/or hand was swollen.

There were 122 women of the 272 women interviewed (44.8%) who stated that they had arm swelling as a result of breast cancer treatment.

Mild - 47 patients (17.2%)
Moderate - 43 patients (15.8%)
Severe - 32 patients (11.7%)

When including all three categories of lymphedema, the probability of remaining lymphedema-free at fifteen years post-surgery was 0.53 (SE = .03). Nevertheless, only 11.7% had lymphedema of the sort that would consistently produce noticeable disfigurement and functional disability of the arm.

Results - time course to development

Questions about time to onset of lymphedema were not successful. In general, patients could not remember a particular year when lymphedema was first noted. They tended to indicate that it occurred soon after the operation. Essentially half of all patients said that lymphedema occurred soon after treatment and, when pressed, stated that the onset could have even been in the first year. It seemed, however, that if the lymphedema occurred closer to the time of the interview, then the patients could be specific about the time.

Considering these the issues, the median time to onset was 1.2 years (range .04 to 18.7 years).

Results - etiology

Clinical, anatomic, pathologic and treatment variables were obtained prospectively and recorded in the pre-existing database from 1976 to 1978. Data concerning arm infection/injury, physical activity, arm activity/exercise, weight change and life events in the follow-up years were obtained by interview.

The prospectively gathered (in 1978-1978) variables are part of the lymphedema database: height/weight at diagnosis, obesity, menopausal status, previous medical history, medications, cancer primary size, number of lymph nodes excised, number/proportion of lymph nodes excised with metastatic cancer.

Several variables present at time of operation in 1976 to 1978 were not collected at that time but were available from review of medical record. These include various specific intraoperative and early postoperative surgical factors: excision of thoracodorsal nerve complex, excision of pectoralis minor muscle, highest level of lymph nodes excised, and specific data on postoperative fluid formation, such as total volume of drainage and number of days with the drain.

Information obtained from interview consisted of weight changes over the interval from diagnosis to the current time, illnesses, operations, medications, hospitalizations (to confirm the pre-existing database information), predominant occupation, hobby, sports in the years since diagnosis (for assessment of general and upper extremity activity level), and arm infection/injury or unrelated arm surgery with detailed data on time of occurrence, length of hospitalization and disability.

See Tables 1a and 1b.

Factors Tested For Relationship To Lymphedema Development

FACTOR	p VALUE
Factors Present at Diagnosis and Treatment	
Physical Characteristics	
Height	.83
Weight	.59
BMI (kg/m2)	.66
Cancer Characteristics	
Number of (+) lymph nodes	.85
Highest (+) in Level I	.37
Highest (+) in Level II	.75
Highest (+) in Level III	.96
Proportion of (+) lymph nodes	.90
Intraoperative Treatment Variables	
Pectoralis Major excised	.49
Pectoralis Minor excised	.14
Thoracodorsal Complex excised	.37
Number of lymph nodes excised	.85
Postoperative Course Variables	
Postoperative infection	.90
Volume of early postoperative drainage	.70
Volume of total postoperative drainage	.72
Duration of postoperative drainage	.83

Table 1A

Factors Tested For Relationship To Lymphedema Development

FACTOR	p VALUE
Factors Present During Subsequent Years After Treatment	
Physical Characteristics	
Current Weight	.13
BMI	.23
Weight Gain**	.01**
Medical Status and General Activity	
Chronic Illness Index	.15
Diabetes Mellitus	.65
Hospitalization Index	.45
Activity Index	.28
Cancer Status	
Contralateral breast cancer treatment	.45
Reconstruction	.85
Specific Arm Factors	
Exercise	.28
Infection/Injury**	.01**

Table 1B

Conclusions

Of all the permanent complications of breast cancer treatment, lymphedema is the most troublesome: The cosmetic deformity can not be disguised with normal clothing, and physical discomfort as well as upper extremity dysfunction is associated with the enlargement. Lymphedema is not always dealt with seriously by clinicians, interested in cancer recurrence, who may unintentionally trivialize the non-lethal nature of lymphedema.

It is estimated that 1-2 million breast cancer survivors are alive today and at least 200,000 of them cope daily with the disfigurement, discomfort and disability of arm and hand swelling. Despite the human cost, lymphedema has not been systematically studied. Nevertheless, before prevention can be discussed, the factors predictive of lymphedema must be known.

Heretofore, there has not been any cohort study or otherwise comprehensive evaluation. Lymphedema has merely been cited among other intraoperative and postoperative complications in various series, along with cancer follow-up. Of the series which attempt to address the issue, none have examined multiple factors in the same study population.[1-5] The scanty scientific evaluation may be due to the view that research issues concerning detection, treatment, and recurrence should take precedence in funding before research issues concerning quality of life.

This is the first cohort study on lymphedema. The number of study subjects (272 women) alone cause this report to be one of the largest on this topic. Approximately half of the data was acquired prospectively. A total of 28 factors were examined.

We have employed an existing extensive data base on a cohort of patients treated consecutively for breast cancer between October 1976 and June 1978 who were known to be free of recurrent breast cancer 10 years after diagnosis. The existing data base includes prospectively acquired information (regarding clinical characteristics, intraoperative factors, pathological factors) and the annually-updated medical and cancer history. The medical records have been reviewed for specific intraoperative and postoperative surgical technique factors that were not part of the original data base but may be associated with lymphedema development. We interviewed survivors for a wide range of factors occurring since her cancer treatment, concerning general activity including predominant occupation, hobby, sports in the years since diagnosis (for

assessment of general and upper extremity activity level), and arm infection/injury or unrelated arm surgery with detailed data. Information on the general health status included weight changes over the interval from diagnosis to the current time, illnesses, operations, medications, hospitalizations (to confirm the pre-existing database information of the annually updated medical history and cancer status. We collected subjective measurements of lymphedema as well as objective self-reported measurements of arm circumferences with a method validated in non-protocol patients.

We found that 32 of 272 (11.7%) long term survivors had severe lymphedema (categorized by a enlargement of 2 inches or more in circumference over the contralateral arm). If those with some measurable lymphedema, but less than 2 inches, are included -- designated as moderate -- then an additional 43 women had lymphedema. Based on these two categories of measurable lymphedema, 75 of 272 (27.6%) have lymphedema. The third category of lymphedema are those who believe that they feel or see arm/hand enlargement although it is not measurable and they have never consulted a medical professional for diagnosis or treatment. If these 47 women are included, then the incidence of lymphedema is 41%.

We found that the time to onset of lymphedema was difficult for women to recall even in general terms, even in the group with severe lymphedema. When the onset of lymphedema was more proximate to the time of interview, the women were definite about its date of onset. There were several women who developed lymphedema between their fifteenth and twentieth year.

Of the twenty-eight factors analyzed, only two were statistically significantly associated with lymphedema: arm infection or injury requiring antibiotics and weight gain since diagnosis.

Women who experienced at least one arm infection or injury requiring prescription antibiotics had a 74% incidence of lymphedema. Women with no infections or injuries requiring antibiotics had a 41% incidence of lymphedema. A caution must be added here because it is possible that the women with lymphedema were more likely to remember the infection/injury and report it to the interviewer.

Women who gained more weight between diagnosis and the current time had a 55% incidence of lymphedema. Women with little or no weight gain had a 30% incidence of lymphedema.

One suspected factor -- the treatment of a contralateral breast cancer -- was demonstrated not to be associated with development of lymphedema. As a matter of fact, those who developed contralateral breast cancer had a lower incidence of lymphedema (38%) versus those who had only the initial breast cancer treatment (51%).

Multiple studies as well as the author's prospective study have suggested postoperative chest wall or breast radiation as a factor. However, there were so few women in this series with postoperative radiation that it was not meaningful to analyze this factor. Furthermore, extent of surgical dissection is usually considered a predisposing factor. It may not have shown an association with lymphedema in this study since these study subjects in the remote time period all underwent a similar, rather extensive axillary lymph node dissection.

In summary, women should again be counseled about avoiding arm and hand infections. Perhaps women should always keep with them small alcohol swabs to quickly treat every break in skin integrity. Furthermore it may not be extreme to suggest that small breaks in skin integrity should be treated with oral antibiotics at time of occurrence with the goal of preventing a clinical infection. Furthermore, even though there are many reasons to refrain from gaining weight, predisposition to lymphedema may be another benefit. Women requiring contralateral breast cancer treatment can be reassured that it should not increase their risk of lymphedema.

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APPENDIX

STATEMENT OF WORK

Lymphedema: Incidence, Time Course, and Etiologic Factors in Long Term Survivors of A Breast Cancer Cohort

Task 1. Months 1-2

a. Final preparatin of data collecting instruments.

b. Pilot study on non-protocol patients seen for routine followup.

Task 2. Months 3 -14

a. Interview of study subjects.

b. Collection of self-reported measurements.

c. Ongoing data entry.

d. Report at Year 1

Task 3. Months 15 - 24

a. Data analysis.

b. Manuscript/report.

Bibliography of all publications, meeting abstracts, and list of personel receiving pay from the negotiatied effort

Publications: none

Publications in which this research project is discussed

1. Petrek JA, Lerner R. Lymphedema: Etiology and treatment. In: Eds. JR Harris, ME Lippman, M Morrow, S Hellman. Diseases of the Breast. 1st Edition. JB Lippincott, Philadelphia, 1995:896-901.

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Meeting Abstracts: none

Personnel

1. Margaret Peters, RN

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